Catalytic asymmetric carbon-carbon bond forming methodologies for synthesis of chiral N-containing heterocycles and chiral carboxamides

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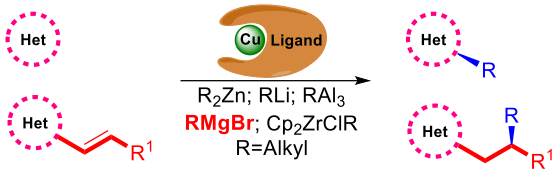
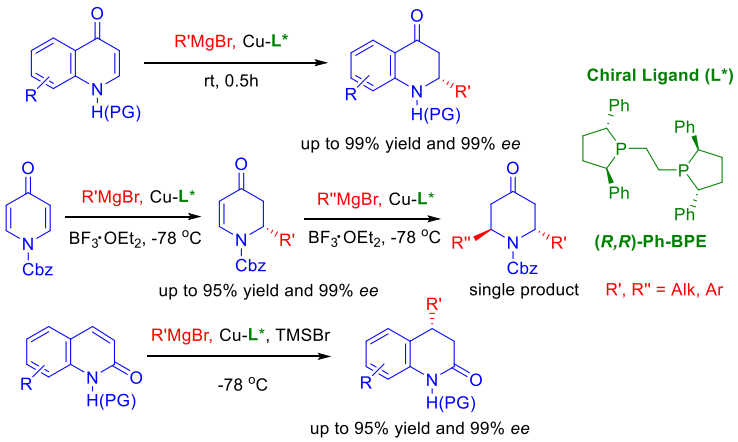
Summary



Chiral heterocycles are ubiquitous structural motifs in natural products and bioactive and pharmaceutical compounds. This has motivated the development of various strategies that target the synthesis of chiral heterocyclic motifs. Catalytic asymmetric addition of highly reactive organometallics could be one of the most straightforward ways to access chiral heterocyclic compounds with high yields and optical purity. Among the various organometallics, Grignard reagents are the most preferred due to their high reactivity, cost efficiency and availability. However, because their high reactivity is difficult to control, there are very few applications of these organometallics in the construction of chiral heterocyclic compounds with high yields and enantioselectivities.

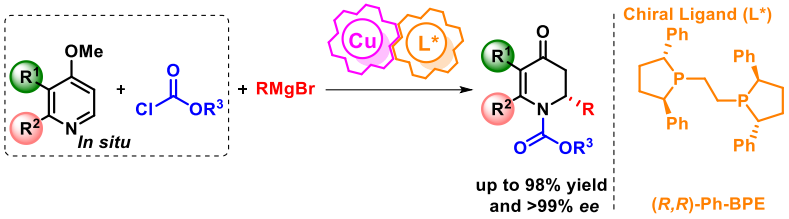
In this thesis, we have developed several strategies that allow the Cu-catalyzed asymmetric conjugate addition of Grignard reagents to various heterocyclic substrates, such as 2-quinolones, 4-pyridone, 2,3-dihydro-4-pyridone, 2-quinolones and *N*-acylpyridinium salts. In addition, we have demonstrated that Lewis acids are highly beneficial for such reactions and can be successfully employed to activate the corresponding acceptors towards nucleophilic additions, as well as control the selectivities in these reactions.

Chapter 2 describes the first general protocol for alkylation of various classes of *N*-heterocyclic electrophiles with organomagnesium reagents, utilizing a single catalytic system based on Cu(I) complex with (*R*,*R*)-Ph-BPE diphosphine ligand. Alkylation of 2-quinolones, 4-quinolones and 4-pyridones provides easy access to various derivatives of chiral 2- and 4-substituted tetrahydroquinolones and dihydro-4-pyridones in excellent yields and enantioselectivities. Significantly, addition reactions to *N*-substituted-4-quinolones can be carried out at room temperature, while consecutive alkylation of pyridone and the resulting 2,3-dihydro-4-pyridones allows for convenient catalytic access to 2,6-substituted diastereomerically and enantiomerically pure piperidones.

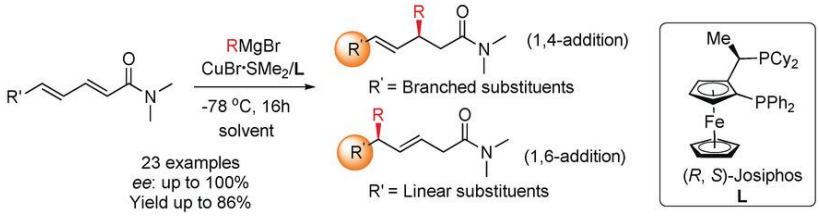


Chapter 3 describes the first catalytic asymmetric addition of Grignard reagents to *in situ* formed *N*-acylpyridinium salts, with excellent yields and *ee*s. The reaction is operationally simple and tolerates a wide range of pyridine derivatives and Grignard reagents and thus has high potential for applications in the synthesis of alkaloids and other complex building

blocks. Finally, computational studies revealed the structural motifs responsible for the transfer of chiral information from the catalyst to the final product.



Chapter 4 describes the first catalytic asymmetric addition of organometallics to various dienyl carboxamides leading to α-, β- or δ-substituted chiral functionalized amides with excellent 1,6- or 1,4-regioselelectivity. The combination of Lewis acid activation and the high reactivity of the reagents lies at the basis of this feat, as this allows to overcome the low reactivity of the amide substrates. Although the substrate structure can strongly affect the regioselectivity outcome we have shown that under our catalytic conditions almost exclusively one regioisomer is formed with excellent enantioselectivity.



Chapter 5 describes the asymmetric conjugate addition of Grignard reagents to bifunctional Michael acceptors bearing a combination of ester, carboxamide, carboxylic acid or pyridine functional groups. It was demonstrated that Lewis acid/base interactions can be used to control/override the reactivity of the dominant functional group, thus allowing regioselective reactions with the less reactive functional group in the presence of a more reactive one without the need for protecting groups.